Embarking on a Chemical Space Odyssey

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Embarking on a Chemical Space Odyssey

Shiao Y. Chow and Adam Nelson*

School of Chemistry and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK

Corresponding author's email address: a.s.nelson@leeds.ac.uk

Abstract:

The chemical space explored in drug discovery programmes is restricted by a narrow reaction toolkit, and the frequent failure of even these reactions with polar and functionalised substrates. Recently, high-throughput reaction optimisation has been integrated into discovery workflows, thereby increasing the value of specific reaction classes in the toolkit. It is likely that high-throughput experimentation will enable expansion of the synthetic chemistry that is widely exploited in discovery, thereby increasing innovation in medicinal chemistry.

Text:

The discovery of bioactive small molecules is an enduring challenge in both medicinal chemistry and chemical biology. Discovery workflows generally involve design–make–test cycles that necessarily rely on the synthetic accessibility of the molecules to be tested. Researchers thus tend to gravitate towards a narrow toolkit[1] of highly reliable transformations which has tended to increase attention on flatter and more lipophilic compounds.[2] Even with this narrow toolkit, reactions involving polar and highly functionalised substrates are systematically more likely to fail, resulting in "logP drift" in which the arrays of produced compounds that are less polar than those designed.[3] In this issue of Journal of Medicinal Chemistry, Cernak and co-workers from Merck describe the application of high-throughput reaction optimisation to expand the diversity of the chemical space that was explored in a drug discovery programme.[4]

Recently, high-throughput experimentation has been adopted by a number of pharmaceutical companies to identify efficient synthetic methods to underpin medicinal chemistry programmes. In 2015, the team from Merck also described the high-throughput, nanomole-scale optimisation of palladium-catalysed cross-coupling reactions.[5] Crucially, the approach enabled the identification optimal conditions for a wide range of couplings

between pairs of highly-functionalised substrates. In the current study,[4] high-throughput experimentation was used to identify reliable reaction conditions for S_NAr chemistry required to underpin the discovery of diacylglycerol acyltransferase 1 (DGAT1) inhibitors.

The starting point for the investigation was a specific benzimidazole lead compound (IC_{50}: 52 nM) (Panel A, Figure). Initial efforts to prepare an array of eight analogues met with limited success: in only four of the attempted S_NAr reactions between the 2-chloro pyridine **E1** and an amine nucleophile was a low (5%-32%) yield of the required product isolated (Panel B, top). As a result, the development of structure-activity relationships (SAR) was significantly hampered.

Next, the synthesis of a further 28 analogues was attempted (Panel B, bottom). In each case, a pair of substrates was reacted under specific reaction conditions (either DIPEA as base in DMA; or K_2CO_3 as base in DMSO). With the 2-chloro pyridine **E1** as electrophile, only 9 of the 19 designed products were obtained, of which only 4 were isolated in >10% yield. The 2-fluoro pyridine **E2** fared better, and all 9 of the designed products were obtained; nonetheless, two of the products were obtained in <10% yield, and the use of DMA at high temperature led to the formation of a 2-dimethylamino pyridine by-product in many cases.

A more systematic approach to reaction optimisation enabled the synthesis of analogues needed to define meaningful SAR. All 24 combinations of six bases and four solvents were screened in the optimisation of the S_NAr reaction between the 2-fluoro pyridine **E2** and the piperidine **N2** (Panel C, top). DIPEA and $NaHCO_3$ were identified as the best-performing bases, having resulted in consistently good conversion with all four solvents. Furthermore, the solvents CPME and NMP were prioritised based on the observed yields and their chemical inertness and solvation ability.

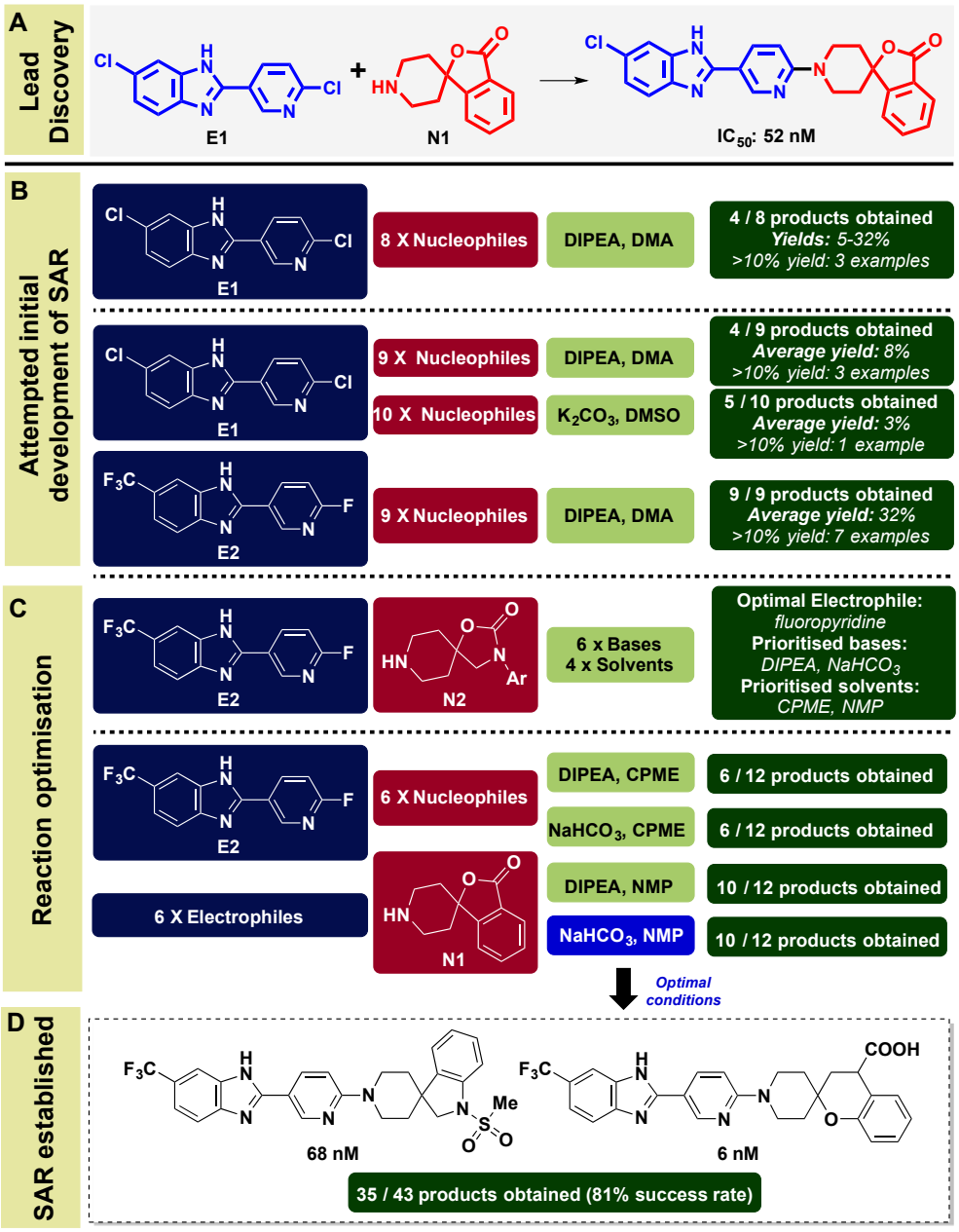

Figure: High-throughput optimisation of S_NAr chemistry, and exploitation of the optimised conditions in analogue synthesis. Panel A: Synthesis of the lead molecule. Panel B: Attempted initial development of SAR using specific synthetic methods. Panel C: Identification of reaction conditions suitable for the synthesis of a wide range of analogues. Panel D: Application of the optimised reaction conditions in the synthesis of a wide range of analogues needed to define SAR.

To identify the robust reaction conditions for the synthesis of a wide range of analogues, the four prioritised base/solvent combinations (DIPEA or $NaHCO_3$ with CPME or NMP) were evaluated with a wider range of substrate combinations (Panel C, bottom). The electrophile **E2** was reacted with six different nucleophiles, and the nucleophile **N1** was reacted with six different electrophiles. With DIPEA or $NaHCO_3$ in NMP, 10 of the 12 substrate combinations

gave an acceptable yield of the required product. Remarkably, neither of these conditions had been optimal in the previous screen of the reaction between **E2** and **N2** (Panel C, top), demonstrating the value of investigating alternative reaction conditions with a range of different substrate combinations.

As a result of the high-throughput reaction optimisation, $NaHCO_3$ in NMP was taken forward, partly because the partial solubility of the base in organic solvents simplified product purification. The optimised conditions enabled the successful synthesis of 35 (of 43) analogues with activities spanning over three orders of magnitude (Panel D). The most potent compound (IC_{50}: 6 nM; MW: 472) was considered an attractive starting point for lead optimisation. Furthermore, the optimised reaction conditions were also exploited in these subsequent lead optimisation activities.

High-throughput reaction optimisation to enable the functional molecule discovery is nonetheless still in its infancy. Published examples of the approach are restricted to the optimisation of reactions that are already in the medicinal chemists' narrow toolkit:[1] for example, Pd-catalysed cross couplings[5] and, now, S_NAr chemistry.[4] The approach has thereby allowed reactions within the established toolkit to be exploited more effectively, and has expanded the range of specific analogues that can be prepared.

Considerable advances are, however, still required in order to increase dramatically the range of innovative high-quality small molecules that may be discovered. For this to happen, the toolkit of reactions actually exploited in discovery workflows needs to be expanded markedly. Remarkably, no new reactions have been added to this toolkit over the last 30 years, despite an unprecedented era of invention in synthetic chemistry. As a result, researchers from AstraZeneca have provocatively asked[1a] where all of the new reactions have gone!

High-throughput experimentation is already helping to address the greater challenge of expanding the reaction toolkit for small molecule discovery. First, screening can identify reactions with high robustness:[6] reactions that are compatible with a wide range of polar and functionalised substrates. Indeed, screening has identified several reactions with high robustness, for example arylations of sp^3-hybridised carbon. Second, an emerging function-driven approach[7] – activity-directed synthesis – deliberately exploits inherently promiscuous reactions. Crucially, activity-directed synthesis can facilitate the discovery of functional small molecules with unexpected structures in parallel with associated synthetic routes.

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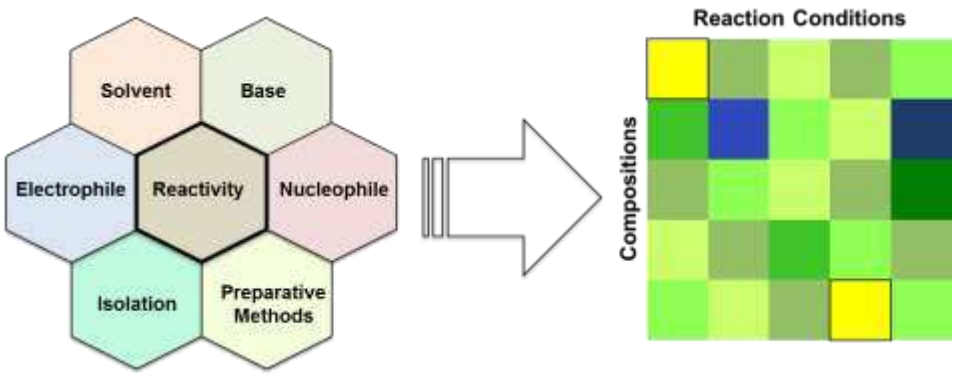
Table of Content Graphic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